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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,109	11/19/2003	Ram I. Mahato	T8948.CIP.2	7310

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THORPE NORTH & WESTERN, LLP.
8180 SOUTH 700 EAST, SUITE 350
SANDY, UT 84070

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,109	MAHATO ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 11/24/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 5/16/07.

This application is a continuation in part of 10/083,861 which is a continuation in part of 09/662,511, now US 6,696,038.

Claims 1-27 are pending and under consideration in this Office Action.

Rejections and objections not reiterated in this Action are withdrawn

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 7, 9, 12, 13, 15, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Puckett et al (US Patent 5,393,335, issued 2/28/95).

Puckett teaches a lubricant consisting of C_2-C_{18} fatty acids linked by amide bonds to polyethyleneimine of molecular weight from 800 to 50,000 Da. See column 3, lines 12-18. An arbitrary fraction of the PEI is considered to be the hydrophilic polymer, and the remainder of the PEI is considered to be the PEI required by the claims. Thus the hydrophilic polymer is bound to the rest of the PEI by a covalent bond. Puckett does not explicitly teach whether or not the lubricant is biodegradable, however it has the same physical structure as that claimed in the claims. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions

are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997).

Claim 6 is included in this rejection because an arbitrary fraction of the PEI can be considered to be the hydrophilic polymer, while the remainder can be considered to be the polycation. Claims 12 and 17 are included in the rejection for a similar reason. One half of the PEI can be considered to be a polycation that is attached at either end to a lipid and to a hydrophilic polymer (i.e. the other half of the PEI). As a result the molar ratio of PEI to hydrophilic polymer would be 1:1. Because the lipid is attached along the length of the PEI molecule, the molar ratio of PEI to lipid would depend on how much of the PEI was considered to be polycation, and how much was considered to be hydrophilic polymer.

Thus Puckett anticipates the claims.

Response to Arguments

Applicant's arguments filed 5/16/07 have been fully considered but they are not persuasive.

Applicant addresses the rejection over Puckett at 7 and 8 of the response. Applicant argues that Puckett does not teach a biocompatible hydrophilic backbone spacer to covalently link the lipid to a PEI backbone. This is unpersuasive because biocompatible hydrophilic backbone spacer has been given its broadest reasonable interpretation, i.e. it corresponds to an arbitrary fraction of the PEI backbone of Puckett. Accordingly, the C_2-C_{18} fatty acid is covalently linked by an amide bond to a segment of

PEI that is considered to be a spacer. That segment is covalently linked to the rest of the PEI backbone which corresponds to the PEI recited by the instant claims. Regarding claims 12 and dependents, one simply and arbitrarily changes the designation of which segment of the PEI is the spacer, and which segment corresponds to the PEI recited in the claims.

Applicant further argues at page 8 that the hydrophilic polymer is not attached to the PEI backbone by a covalent bond. This is incorrect for the reasons set forth above. Clearly if PEI is one molecule, the atoms in that molecule are joined by covalent bonds. Any arbitrarily selected C-C bond in the PEI backbone can be considered to be the covalent bond joining the hydrophilic polymer spacer to a PEI.

For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cullis et al (US Patent 6,852,334) in view of Godbey et al (J. Contr. Rel. (1999) 60: 149-160).

Cullis taught cationic-polymer-lipid conjugates of the general formula A-W-Y, wherein A is a lipid moiety that acts as a lipid anchor, W is a hydrophilic polymer, and Y

is a polycationic moiety. See column 2, lines 43-51. The lipid can be a diacylglycerol comprising fatty acyl chains of 2-30 carbons. See column 4, lines 38-41. The hydrophilic polymer can be PEG of 250-7000 Da. See column 13, lines 11-16. The polycationic moiety can be a linear or branched polyamine (column 13, lines 21-26), and can have an attached targeting antibody. See column 14, lines 6, 7, 10, and 14. The complexes are intended to be used for the delivery of nucleic acids. See abstract and e.g. column 15, lines 55-63. The components of the conjugate are joined by amid or ester bonds, see paragraph bridging columns 13 and 14. Helper lipids such as DOPE are used in the conjugate compositions. See entire document, e.g. column 3, lines 49-50.

Although Cullis suggested linear or branched polyamines as polycations, Cullis did not explicitly teach the use of PEI as a polycation.

Godbey taught that PEI is a polyamine polycation that will spontaneously adhere to and condense DNA to form complexes that are readily endocytosed by cells, and that PEI buffers endosomal pH, thus allowing cytoplasmic release of DNA prior to lysosomal degradation. See page 157, column 2, first full paragraph. Godbey taught that the optimal molecular weight was about 25 kDa, and that both linear and branched forms were used. See page 150, column 2, lines 6-11, and page 153 at lines 1-11 of paragraph bridging pages 153 and 154.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use PEI as a polycation in the invention of Cullis. One would have been motivated to do so in view of the art recognized utility of PEI as a nucleic acid

condensing and delivery agent, and the fact that the compositions of Cullis are intended for use in delivering nucleic acids. The ratios of PEI to hydrophilic polymer and lipid, and the ratio of lipopolymer to targeting moiety, and the N/P ratios of nucleic acid/conjugate complexes are considered to be result effective variable that are routinely optimized by those of ordinary skill in the art.

Claims 12-21, 24, and 25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Epand et al (US Patent 5,283,185, issued 2/1/94) in view of Ogris et al (Gene therapy (1999) 6: 595-605).

Epand taught methods and lipopolymeric compositions for transferring nucleic acids into cells. See abstract, claims 1 and 10, and compound XV, described at column 9, lines 45-58. Lipopolymeric compound XV is formed by mixing cholesteryl chloroformate with PEI 600. The resulting reaction chemistry is identical to that taught in the instant application, and results in the formation of a lipopolymer with cholesterol covalently bound to PEI via an ester linkage. Compare Fig. 1 of the instant application with Fig. 3 of Epand. The composition may comprise a DOPE helper lipid in a 1:1 ratio with the cationic lipopolymer. See Table I at column 12, and column 12, lines 58-61. Epand teaches that the charge ratio of lipopolymer to nucleic acid is a result effective variable. See column 13, lines 6-11, and Fig. 5.

Epand did not teach PEI covalently modified with a biocompatible hydrophilic polymer or a targeting ligand.

Ogris taught DNA/transferrin/PEI/PEG complexes in which PEG and transferrin were independently covalently attached to primary amines of PEI. The PEG has a molecular weight of 5000 D. Approximately two thirds of the primary amino groups of PEI remained unmodified. See abstract; and paragraph bridging pages 595 and 596. Ogris taught successful delivery to tumor cells in mice by systemic administration of the complexes.

It would have been obvious to one of ordinary skill in the art the time of the invention to graft PEG to the branched lipopolymer of Epand et al, as well as to attach a targeting ligand such as transferrin. One would have been motivated to do so because Ogris teaches that covalent attachment of PEG to DNA/PEI complexes improves DNA delivery in vivo. See abstract and first paragraph on page 595, column 1. It would have been similarly obvious to optimize the N/P ratio of a nucleic acid complex comprising the lipopolymer, as well as the amount of targeting ligand incorporated into the complex, as each of these will clearly affect the performance of the complex.

Claims 12-15, 17-21, 24, and 25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Epand et al (US Patent 5,283,185, issued 2/1/94) in view of Godbey et al (J. Contr. Rel. (1999) 60: 149-160).

Epand taught methods and lipopolymeric compositions for transferring nucleic acids into cells. See abstract, claims 1 and 10, and compound XV, described at column 9, lines 45-58. Lipopolymeric compound XV is formed by mixing cholesteryl chloroformate with PEI 600. The resulting reaction chemistry is identical to that taught

in the instant application, and results in the formation of a lipopolymer with cholesterol covalently bound to PEI via an ester linkage. Compare Fig. 1 of the instant application with Fig. 3 of Epand. The composition may comprise a DOPE helper lipid in a 1:1 ratio with the cationic lipopolymer. See Table I at column 12, and column 12, lines 58-61. Epand teaches that the charge ratio of lipopolymer to nucleic acid is a result effective variable. See column 13, lines 6-11, and Fig. 5.

Epand did not teach PEI covalently modified with a biocompatible hydrophilic polymer or a targeting ligand.

Godbey taught that PEI may be covalently modified with PEG for the purpose of extending its half life in vivo. See paragraph bridging columns 1 and 2 on page 153. Additionally, Godbey teaches that PEI has been coupled to a variety of ligands for the purpose of cell targeting, including galactose and transferrin, and notes that ligands which have been successfully used in poly(L-lysine)/DNA complexes should be useful in PEI/DNA complexes as well. Such ligands include low density lipoprotein. See paragraph bridging pages 154 and 155. Godbey reviewed the use of PEI in gene delivery methods, and noted that PEIs ranging in molecular weight from about 8000 to about 1,000,000 are useful for gene delivery. See page 121, paragraph bridging columns 1 and 2; and Fig. 2 on page 151. Godbey also taught that the molecular weight of PEI in such complexes is a result-effective variable, and that the ratio of PEI amine to DNA phosphate is also a result-effective variable. See page 153, column 1, second and third full paragraphs; and lines 1-6 of the paragraph bridging pages 153 and 154.

It would have been obvious to one of ordinary skill in the art the time of the invention to covalently modify the PEI of Epand with PEG in order to increase its half life in vivo, and to attach targeting ligands to PEI in order to improve the specificity of nucleic acid delivery. It would have been similarly obvious to optimize the N/P ratio of a nucleic acid complex comprising the lipopolymer, as well as the amount of targeting ligand incorporated into the complex, as each of these will clearly affect the performance of the complex.

Response to Arguments

Applicant's arguments filed 5/16/07 have been fully considered but they are not persuasive.

Applicant addresses the rejection over Cullis in view of Godbey at pages 9 and 10 of the response.

Applicant argues that one of ordinary skill in the art would not have been motivated to combine these two references because Godbey teaches uptake of toroidal complexes whereas Cullis teaches uptake of liposomes, and these uptake processes are different. Applicant places much weight on Cullis' use of the term "fusogenic" in describing the liposomes. However, it is clear from column 6, lines 9-14 that "fusogenic" refers to the ability of a liposome or other drug delivery system to fuse with any membrane of a cell, not limited to the plasma membrane. The membranes can be membranes surrounding organelles, e.g. an endosome. Further Cullis explicitly taught the attachment to the polycation of a targeting antibody. See column 14, lines 6, 7, 10,

and 14. As Applicant may be aware, the use of such antibodies targeted to cell surface proteins results in an endocytic, and not fusogenic mechanism of uptake. Furthermore, Applicant has presented no evidence that the complexes of Cullis, even without targeting ligands, must be taken up by a fusion mechanism rather than by endocytosis. The fact that the liposomes may contain fusogenic lipids does not mean that the liposomes cannot be taken up by endocytosis upon contact with the cell membrane. Accordingly, Applicant's argument that that the two references require different uptake mechanisms is unpersuasive.

Applicant appears to argue that there would have been no reasonable expectation of success in using a PEI backbone in a liposomal due to the high solubility of PEI and the inherent difficulties in forming the liposomes of Cullis. This is unpersuasive because the invention of Cullis need not take the form of a liposome. See column 15, lines 55-61 in which Cullis states that the cationic polymer-lipid conjugate (CPL) can be in the form of a micelle, a lipid-nucleic acid particle, or a nucleic acid aggregate. Even if the invention of Cullis did need to be in the form of a liposome, Applicant has not provided sufficient evidence that one could not reasonably expect success when using PEI as a polycation due to its solubility. There is no evidence to suggest that PEI is any more soluble in water than e.g. the cationic dendrimer or polycationic peptide of greater than 2 positive charges disclosed at column 13, lines 17-25. Applicant's reliance on Godbey, citing Oku, to provide evidence of the unpredictability of the effect of PEI on liposome stability is misplaced. The paragraph referred to clearly indicates that PEI did not cause any lysosomal instability when used

at concentrations used to transfect cells, and that although PEI was found by Oku to destabilize phosphatidylserine (PS) liposomes, this effect was not seen in liposomes containing both PS and phosphatidylcholine (PC). Thus one of ordinary skill in the art would clearly know how to mitigate the effects of PEI on PS liposomes, i.e. by adding PC to the liposomes. Further, one of ordinary skill in the art could simply make liposomes that did not contain PS, e.g. PC or PC/cholesterol liposomes as taught by Cullis at e.g. Tables 2 and 3 at columns 27 and 28. Thus Applicant has presented no valid reason to doubt that one of ordinary skill in the art would have had a reasonable expectation of success in combining the references.

Applicant addresses the rejection over Epand and Ogris at pages 10 and 11 of the response. Applicant appears to argue at page 10 that it would not be obvious to use medium size and smaller PEIs in the invention of Ogris (corresponding to PEI of 50-20,000 Da as in claim 5?) because these PEIs would reversibly dissociate fro Ogris-type PEGylated nanoparticles during PEGylation. This is unpersuasive because it is only an opinion and lacks evidentiary support. Applicant argues that one of ordinary skill would not have been motivated to combine the references because Ogris stated that "PEGylating PEI for complex formation is not used in order to prevent the undesired effects of PEG modified polycations on the DNA condensation process." This is an apparent reference to the passage at page 595 in Ogris in which it is indicated that PEGylation of PEI was not performed until after complex formation with nucleic acids. It is unclear why this would adversely affect the motivation of one of ordinary skill in the art to combine the references, because it is unclear why one of ordinary skill would not

form DNA complexes with the lipopolymeric conjugate of Epand, and subsequently PEGylate these complexes, as taught by Ogris. This would result in the claimed compositions.

Applicant addresses the rejection over Epand and Godbey at pages 11 and 12 of the response, essentially reiterating the arguments raised against the combination of Cullis and Godbey. These arguments are unpersuasive for the same reasons set forth above, i.e. Epand, like Cullis, does not require liposomes. See Epand at column 3, lines 7-21 in which it is clear that the cationic lipid of Epand is used in a "mixed dispersion" to form a complex with a nucleic acid. The word "liposome" is never mentioned. Accordingly, arguments that rely on the requirement for liposomes are unpersuasive. For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635